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Requesting a complete biosensor system in phyto-sourced drug discovery and development

Md. Torequl Islam[1,3]*, Bishwajit Guha[1], Mohammad Ashab Uddin[1], Rahul Mutsuddy[1], Aunamika Khastagir[2], Mohammad Shajid Ashraf Junaid[1], Ana Amélia de Carvalho Melo-Cavalcante[3], Rivelilson Mendes de Freitas[3]

[1]*Department of Pharmacy, Faculty of Science and Engineering, Southern University Bangladesh. 22-Shaheed Mirza Lane (E), 1st floor, Academic building-II, Mehedibag road, Mehedibag-4000. Chittagong, Bangladesh.*
[2]*Department of Biochemistry & Biotechnology, Faculty of Basic Medical and Pharmaceutical Science, University of Science and Technology, Chittagong, Bamngladesh.*
[3]*Department of Biochemistry and Pharmacology, Post-graduation Program in Pharmaceutical Science, Federal University of Piauí, 64.049-550, Teresina, Brazil.*

Abstract: *Constituents from plant origins constitute about 25% of prescribed drugs in modern medication library. But the time taken from discovery to reaching the clinical therapy for a new drug in this field is approximately 12 years. In the modern scientific world, biosensors could lead to groundbreaking and positive changes in drug discovery and development with the potential applicability and advantageous facts coined as simplicity in use, higher sensitivity, rapidity, potential miniaturization, ease of handling, portability and economy: in comparison to well-established, lab-based conventional methods. Keeping a hope that biosensory can be an impending weapon in the phytomedical field of research, the present study is carried out through a comprehensive and systematic bibliographic search in articles and patents in the databases namely - Science Direct, Scopus, Pub Med, Web of Science, INPI, EPO, WIPO, USPTO, CIPO, and miscellaneous. As per acquired results, it is evident that there is no direct link to a complete phytotherapeutic research conducted using biosensors but the successful use of biosensors in other fields reflects a possibility of it making a tuneful continuation in the field of phyto drug discovery and development.*

Keywords: *biosensors, implementation, phytomedicine, request, search.*

I. Review rationale

The biosensor was first described by Clark and Lyons [1], when the term enzyme-electrode was introduced for glucose estimation in a sample. Now it's been a popular technique due to the greater sensitivity, economy, ease of preparation, moderation and sampling, and wide range of applicability. Conventionally, biosensors have been defined as responsive systems consisting of two parts; a biological part; which is used to detect chemical or physical changes in the environment, and an electronic component that essentially transduces the signal into an electronic device, where it is measured and quantified.

Drugs from mineral, plant and animal origins (natural products) with therapeutic properties are as ancient as human civilization itself. For a long time, these have been the main sources of drugs drugs.[2] A very high percentage, which is about 25% of the drugs those have been prescribed worldwide come from plants and among them 121 active compounds are in current use. Of the 252 drugs considered as basic and essential by the World Health Organization [3], 11% originate exclusively from plants. Drugs derived from plants better to be termed "phytomedicines" are now very popular in developing countries due to their safety, efficacy and quality as reported by Calixto [4]. In modern days, alternative therapies and the therapeutic use of natural products, especially those derived from plants are gaining focus. And this is due to the inefficiency of conventional medicines (e.g. side effects and ineffective therapy), abusive and/or incorrect use of synthetic drugs resulting in side effects and concurrent problems, inaccessibility of conventional pharmacological treatments to people of all class. On the other hand, in case of folk medicine, research suggests that they are harmless.[5]

The term "Phytomedicine" can be defined in a number of different ways. In general, it is the medicine obtained through crude extraction from single and/or multiple parts of the plants, solvent fractions, partially fractioned phytochemical mixtures, and plant extract prepared from combination of several medicinal plants or parts of them. Traditional medicines in world-wide are prepared this way. Although the industrial revolution and the development of organic chemistry resulted in synthetically produced medicine being preferred but to develop new drugs is a complex, time-consuming, and expensive process. Essentially, the new drug discovery involves the identification of new chemical entities (NCEs), having the required characteristic of druggability and medicinal chemistry.

The approach, however, was proven to be less effective in terms of overall success rate. The time taken from discovery of a new drug to its reaching the clinic is approximately 12 years, involving more than 1 billion US$ of investment in today's context context.[6] After going through the evidences, it is clear that biosensors have promising capability in assorted fields like physical, chemical and the elaborated branch of biology termed as biomedical encompassed analysis followed by affable diagnosis and treatments. Surprisingly, there are no direct and/or complete evidences for an inclusive phytochemical research.

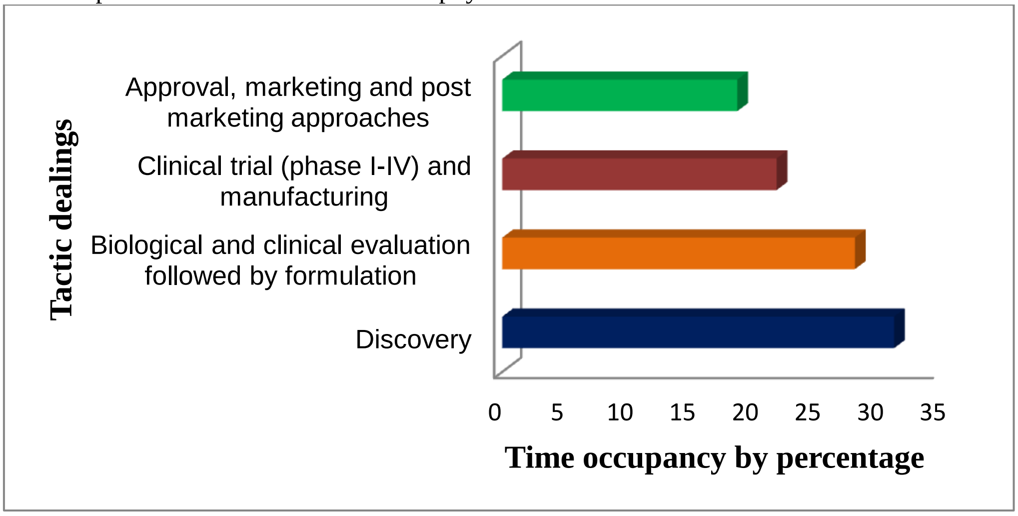

Figure 1. Possession time in percentage for the discovery and development of drugs from plant origin

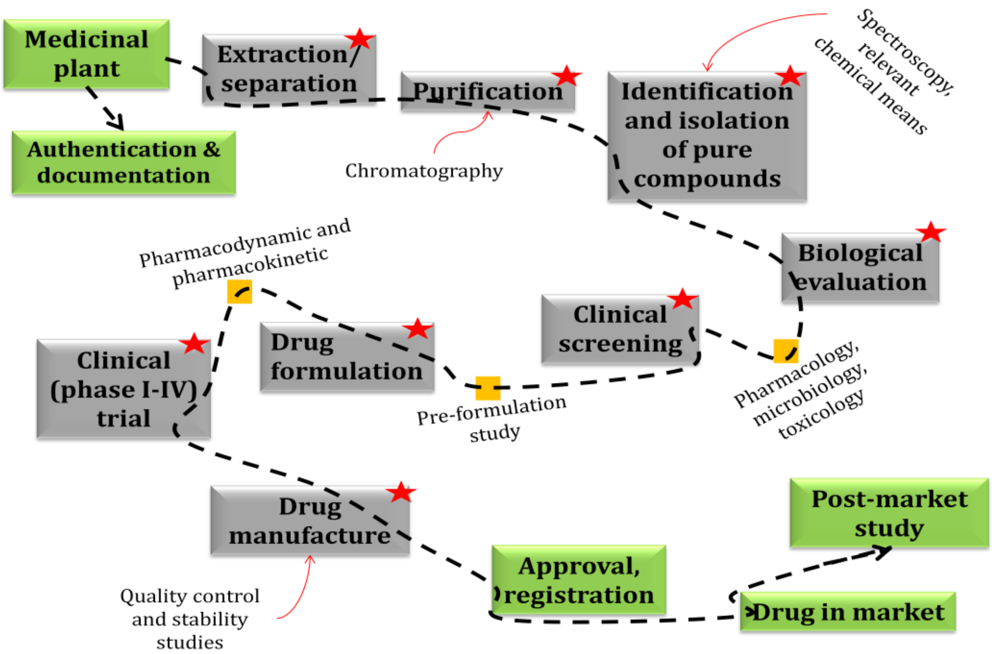

Figure 2. Overall action strategy of phytomedicine discovery and development [ash print with staric marks indicating the critical time consuming steps as it goes to the occupancy time by 71.88%; it also indicates the possible nodes for implication of biosensorization]

From the graphical presentation (**Figure 1**) it is evident that phytochemists have to spend 71.88% time (11.5 years out of 16 years) during the phases starting from extraction to clinical screening (marked with stars; (**Figure 2**) phases. But after going through the currently existing evidences we can be hopeful of speeding up the overall process. The aim of the present study is to contemplate the biosensory concepts in phytomedicines after an effectual screening of the earlier reports.

II. Study design in short

The current research work has been accomplished through of an inclusive and systematic bibliographic electronic search for acquaintance in internet. The Search was made to look for available articles and patents. The articles were searched in databases of Science Direct (SD)[7], Scopus (SP)[8], Pub Med (PM)[9], Web of Science (WS)[10] and Miscellaneous (MIS) (e.g. - google, eBay, MNSi)[11] publications. Then the patent search was performed in the database of the National Institute of Industrial Property of Brazil (INPI)[12], European Patent Office (Espacenet: EPO)[13], World Intellectual Property Organization (WIPO)[14], United States Patent and Trademark Office (USPTO)[15] and Canadian Intellectual Property Office (CIPO)[16]. The periodicity of this research was performed in December 2014. A flowchart showing the steps of realization of this research is shown in **Figure 3**.

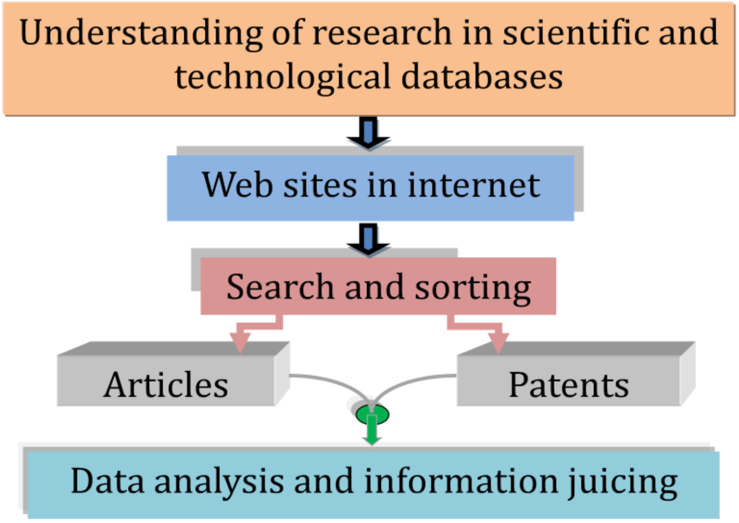

Figure 3. Schematic diagram of intellectual research

Search was made following the topics mentioned – biosensors in phytomedicines, phytochemical analysis, phytochemicals research and phytotherapy, biosensors and its applications, biosensors and its forecasting, modern biosensors and biosensors in phytochemical and related fields. The systematic information as periodicals, articles, patents were considered as raw data. After consequential sorting and understanding, a final result was configured. As the number of published articles and patents are more than 385, only the web portal addresses have been provided.

III. Revision findings

According to **Table 1**, the 'search topic', biosensory in phyto-research hit 214 articles and 173 patents in the web results. There were no articles and patents directly linking to the search topic 'biosensors in phytomedicines'. Only the closely related and/or implementable modal substantiations were considered as data in this research.
Among 214 articles found through the portals; SD, SP, PM, WS and MIS where the distribution was 148, 10, 18, 5 and 33 respectively

Table 1. Prospection of biosensory in similar and/or related phyto research fields[7-16]

Number of articles in web searched					Number of patents in web searched				
SD	SP	PM	WS	MIS	INPI	EPO	WIPO	USPTO	CIPO
148	10	18	5	33	4	20	45	22	82

SD: Science Direct; SP: Scopus; PM: Pub Med; WS: Web of Science; MIS: Miscellaneous INPI: Institute of Industrial Property of Brazil; EPO: European Patent Office (Espacenet); WIPO: World Intellectual Property Organization; USPTO: United States Patent and Trademark Office; CIPO: Canadian Intellectual Property Office.
Source: Authorship Own (Dec. 2014).

Patents screened according to their applicability in phytomedicine research (Table 2), tells a maximum of 82 patents were coined in CIPO, followed by 45, 22, 20 and 4 in WIPO, USPTO, EPO and INPI, respectively. As the number of biosensory evidences is increasing day by day in the research fields related to the contemplated one, (phytomedical) we can be hopeful that we will find a successful and complete phytobiosensory in the near further.

Patents found in data base on biosensors related to phyto, drug discovery and development and other fields are listed in the **Table 2,** while Table 3 has been configured to represent the applicability of the biosensor systems found in table-2 in the area of phytomedicine research.

Table 2. Number of patents found in database with their applicable areas.[12-16] *Source: Authorship Own (Dec. 2014).*

Fields	Patent number/publication year				
	CIPO	**WIPO**	**EPO**	**INPI**	**USPTO**
Chemicals and biochemicals identification, isolation and analysis	CA2353535/2000; CA2353419/2000; CA2702977/2009; CA2787483/2011; CA2660129/2008; CA2632992/2007; CA2446965/2002; CA2725615/2010; CA2448713/2002; CA2529300/2004; CA2603542/2006; CA2471863/2003; CA2625327/2007; CA2553632/2005; CA2535095/2006; CA2518423/2004; CA2506513/2004; CA2482689/2003; CA2436206/2002; CA2275541/1998; CA2545006/2005; CA2420584/2008; CA2226357/2002; CA2861752/2009; CA2637640/2008; CA2450109/2003; CA2419019/2002; CA2465048/2003; CA 2506911/2004; CA 2372175/2000	US2706120/2014; US6319668/2001; US0261136/2013; US0149530/2009	US311922 (A1)/2014; RO129797(A2)/2014; US248710(A1)/2014; TW19558(A)/2013; KR0066611(A)/2013; US177924 (A1)/2013; HK1120568(A1)/2012; EP2776573(A1)/2014; CN202330280(U)/2012	PI 0707502-2 A2/2007; PI 0202977-4 A2/2002	US0312684A1/2012; US0338046A1/2013; US0177518A1/2011; US0186433A1/2011; US0224760A1/2013
Tests for carbohydrates	CA2865120/2013; CA2696783/2013; CA2600132/2006; CA2160905/1994; CA2471889/2003; CA2472108/2003; CA2160905/1994; CA2042373/1991; CA2625165/2007		CA2865120(A1)/2013; US127137(A1)/2014; KR0107003(A)/2013; IL190706(A)/2012; US229916(A1)/2011; EP2426485 (A1)/2012	PI 0607841-9/2006	US0028319A1/2012; US0143659A1/2009; US0155180A1/2006
Screening for microbial contamination	CA2557612/2005; CA2557612/2005	US0170263/2014; US0105421/2011; WO114810/2009; US0130128/2009; WO0092624/2009; WO026166 /2009; WO026176/2009; WO026179/2009; CA2696753/2009	US322790(A1)/2014; US303012(A1)/2014; KR0088202(A)/2012; US156688(A1)/2012; US135437(A1)/2012		

Histochemical analysis	CA2765314/2010; CA2752671/2010; CA2614507/2006; CA2193318/1997; CA2625169/2007; CA2398583/2001; CA2823440/2012; CA2730544/2010	EP2660592/2013		PI 0600263-3 /2006	US0259946A1/2013; US0244339A1/2011; US0286760A1/2008
Pharmacological and clinical investigations	CA2648263/2007; CA2603542/2006; CA2510876/2005; CA2173461/1995; CA2782858/2011; CA2609573/2006; CA2398583/2001; CA2202893/1996; CA2608988/2006; CA2507323/2006	WO070324/2013; US0315324/2012; WO097480/2011; WO0177156/2011; WO094172/2009; CA2712757/2009; WO064696/2009; CA2705797/2009; US0093557/2014; US0308212/2014; WO051287/2012; US0263504/2011; WO0172234/2011; US0117121/2011; US0117121/2011; WO127302/2008; WO127302/2008			US0228547A1/2014; US0013334A1/2013; US0280736A1/2013; US0270326A1 /2012; US0241054A1/2010; US0116405A1/2013; US0275134A1/2011
Tests for proteins	CA2545006/2005; CA2518423/2004; CA2482689/2003; CA2557623/2005; CA2569401/2005; CA2448713/2002; CA2418724/2002; CA2324662/2002; CA2290898/2001; CA2245664/1997; CA2255952/1997; CA1313828/1987; CA2682325/2008; CA2524585/2004; CA2645957/2007	US0262198/2008; WO110015/2005; CA2573918/2005; WO106374/2004			US0235831A1/2014; US0210257A9/2011; US0298706A1/2009
Drug manufacturing	CA2667061/2008; CA2547537/2009; CA2547317/2005; CA2427033/2002; CA2708445/2009; CA2531118/2005; CA2510885/2005				
Drug delivery		WO054026/2014; WO162729/2013; US6100026/2000; US5961923/1999			
Preparation of herbal medicines		US0287115/2011; US0038196/2008			

Mixing/homogenizing					US0189421A1/2013
Phytochemicals aided biosensory	CA 2393816/2001				

Table 3. Number of publications and patents cited in data bases

Biosensory related and/or applicable to -	**Articles in journals**					**Patents in intellectual properties**				
	PM (18)	***SD (148)***	***SP (10)***	***WS (5)***	***MIS (33)***	***INPI (4)***	***WIPO (43)***	***CIPO (82)***	***USPTO (22)***	***EPO (20)***
phytochemical identification	2	21	1	0	8	1	2	9	4	9
phytochemical isolation and /or charaterization	6	22	0	0	3	1	2	28	4	0
screening activity for phytoconstituents	3	15	4	0	6	1	22	10	2	5
drug discovery, design and/or manufacturing with phytoconstituents	4	35	5	3	6	0	2	8	1	0
clinical trials of phytoconstituents	3	46	0	1	8	1	13	27	11	6
phytochemical based pharmaceutical manufacturing	0	9	0	1	2	0	0	0	0	0

SD: Science Direct; SP: Scopus; PM: Pub Med; WS: Web of Science; MIS: Miscellaneous INPI: Institute of Industrial Property of Brazil; EPO: European Patent Office (Espacenet); WIPO: World Intellectual Property Organization; USPTO: United States Patent and Trademark Office; CIPO: Canadian Intellectual Property Office.

Source: Authorship Own (Dec. 2014).

3.1. Biosensors in compound identification

Research on phytomedicine, chromatographic techniques such as thin layer chromatography (TLC), gas chromatography (GC) and high performance liquid chromatography (HPLC) are commonly used to obtain a characteristic fingerprint profile that ensure the presence of a particular chemical constituent in the sample tested. However, the conventional separation and detection methods are time consuming, expensive and largely dependent on the polarity of the mobile phase (TLC and HPLC) and volatility of the compounds (GC) to be separated. Ahmad et al [17] had successfully equipped an in-house multichannel devise consisting of artificial lipid-polymers and successfully obtained the fingerprint of the chemical moieties of *Eurycoma longifolia* crude extractives. Later, Later, Babu et al [18] and Akyilmaz and Turemis [19] introduced two biosensors with distinct mechanisms to determine caffeine (alkaloid) in a sample solution. Whole-cell technique utilizing bacteria, fungi, yeasts, animal or plant cells can be equipped as biosensors to detect a number of chemicals chemicals.[20,21] Aptamers (single-stranded DNA or RNA oligonucleotides) having the ability to bind to a wide range of target molecules can be projected for the identification of adenosine, cocaine, aromatic amines, ATP, theophyllin, arginine, neomycin, flavin mononucleotide, streptomycin, tetracycline, biotin, moenomycin A, S-adenosylhomocysteine, oxytetracycline, codeine, cholic acid, and dopamine.[22] Nanomaterials modified with DNA (deoxyribonucleic acid) probes has been successfully targeted for heavy metal detection (e.g - Hg^{2+}, Pb^{2+})[23] can also be targeted for the detection of the possible contamination occurring due to heavy metals. As shown in **Table 3** it is evident that we can not overlook the possibility of incorporating biosensors in this phytomedical step.

3.2. Biosensors in compound isolation

Extraction of volatile oils from plant origins has always been time consuming and expensive. On top of that it becomes very difficult to handle the temporal volatile components. But insects having higher sensitivity to detect volatile substances, a rapid volatility analyzer biosensor, electronic nose has been commenced by Fernández-Grandon et al [24]. After that an ultrasensitive fluorimetric biosensor for the detection of chemical warfare agent sulfur mustard (SM) was developed using its mono-functional analogue.[25] In addition to the enzyme-electrode system, novel and sensitive assembled quantum dots (QDs)–bienzyme (glucose oxidase (GOD) and horseradish peroxidise (HRP)) hybrid system was designed for the direct determination of glucose.[26] As per data represented in **Table 3**, biosensorism can be tracked in this critical step of phyto-research.

3.3. Biosensory in screening study

An in vitro antioxidant test of plants (*Salvia officinalis*, *Achillea millefolium, Origanum vulgare* and *Gentiana lutea*) crude extracts was introduced in a laboratory-made biosensor based on immobilized fibroblast cells producing a hyperpolarization to the membrane of the cells, which resulted a more rapid response (within 3 min) in comparison to the conventional DPPH (1, 1 diphenyl 2 picrylhydrazyl) scavenging spectroscopic method.[27] Li et al [28] developed a lateral flow assay (LFA) for the detection of whole-cell antigens of *Pseudomonas aeruginosa* and *Staphylococcus aureus* based on the use of gold nano-particles (AuNPs) functionalized with specific antibodies as labels. After that Preechakasedkit et al [29] developed an LFA based on immunosandwich with AuNPs for the detection of *Salmonella typhi* in human serum. A very interesting device was proposed by Kim et al [30] combining a microfluidic reverse transcription polymerase chain reaction (RT-PCR) reactor with a LFA to detect H1N1 virus. Recently another biosensory method inhibiting quorum sensing-controlled virulence factors has been introduced with successful inhibition to the pathogens, *Chromobacterium violaceum* and *P. aeruginosa*.[31] The later one also has been drawn in successfully to detect bacterial impact on pathogenicity, food spoilage and producing antipathogenic compounds compounds.[32,33] However, search evidences tell us that biosensorism is mainly in practice in the fields of pharmacological and clinical investigations; therefore, on the basis of collected information (**Table 3**) the use of biosensor systems in detailed investigation for phyto-constituents is recommended.

3.4. Phytochemicals aided biosensory

Green chemistry, a sustainable initiative to improve and/or protect global environment is now the focal issue in the field of research. That is why the constituents from plant origins having antioxidant properties are being applied in a noble-broad sense in nano-synthesis. Ahmad and Sharma [34] have introduced and proposed the reduction mechanism of silver ions (Ag^{+1}) to silver nanoparticles (AgNPs) with a range of <5 to 35 nm. Where they demonstrated that the plant, *Ananas comosus* containing two antioxidants namely- ferulic acid and chlorogenic acid reducing aqueous silver nitrate to neutral AgNPs. A similar study has been done by Hazarika et al [35] with the crude organic (hexane and ethanol) extracts of the plant, *Rhynchotechum ellipticum* to synthesize AgNPs in spherical shape with an average size in the range of 510 to 730 nm.

3.5. Forecasting biosensory in phytomedical research

As paper based biosensory has been proven for its potential successful application in detection of proteins, nucleic acids and cells [36,37] we can apply this sense to detect and isolate protenous active principles like hemp (recently using as a nutritional supplement; obtained from Cannabis plant) which is rich in protein (about 30.6%).[11]

3.6. Biosensors targeted for pharmacological and clinical investigations

A number of biosensory techniques are now available for clinical investigation of pathologic conditions; those can be targeted for pharmacological, toxicological and clinical screening of constituents streaming from plants. A list has been given in **Table 4**.

However, data depicted in **Table 3** represents the applicability of a good number of biosensorism in this critical step.

Table 4. New biosensors targeting clinical investigations that have appeared in the literature for several biomarkers

Detection followed by investigations	Biorecognition element/biosensory	Tracked by (ref.)
Anticancer	ACA, ASA, ADA, DNA	[37,38]
Cardiovascular (CVS)	ApSA, Ap, ADA, ASA	[37,39]
Hepatoprotective/hepatotoxicity	DNA, PNA, MBS	[37,40]
Anti-inflammatory	ASA	[37]
PNS mediated stress	ACA	[37]
Antimicrobial	ACA, ASA, OS	[36]
Antiatherothrombosis	ACA, ASA	[41]
Antioxidant	WCI	[27]
Anti-genotoxicity	WCI	[42]

ACA: Antibody competitive assay; ASA: Antibody sandwich assay; ADA: Antibody direct assay; Ap: Aptamer; ApSA: Aptamer sandwich assay; MBS: Microcantilever based sensors; DNA: deoxyribonucleic acid; PNA: Peptide nucleic acid; OS: Optical sensing; PNS: Peripheral nervous system; WCI: Whole cell induced.
Source: Authorship Own (Dec. 2014).

3.7. Biosensory in pharmaceutical manufacturing

Dendrimers (hyperbranched, monodispersed, star-shaped, and nanometer-scale three-dimensional macromolecules with a very high density of surface functional groups) have been used extensively in various biosensors and diagnostics, such a concept can be incorporated into drug delivery, gene transfection and catalysis. Lipid vesicles, thin lipid films, and liposomes are biological nanomaterials (NMs) formed via the bottom-up nanotechnology approach. Having similar composition to the cell membrane, they must be considered as biocompatible materials, and thus can be employed for the rapid diagnosis of biochemicals, drug-protein interactions, colorimetric analysis of drugs, bacterial counting and quantitative electrolytic assay.[43] For analysis of a number of pharmaceutically important drugs, a few biosensors have been established, those are listed below in **Table 5**.

Though only 3 publications have been found on this critical search topic, bionsensorism has the potential of being used extensively in pharmaceutical industries in upcoming days (**Table 3**).

Table 5. Biosensors in the pharmaceutical analysis (Gil and Melo, 2010)

Drugs/agents	Biosensory
Salicylates	Electronic, salicylate hydroxylase (SH), modified SH
Acetaminophen	Enzyme linked biosensory (HRP)
Catecholamine	Enzyme linked biosensory (HRP), whole cell biosensory
Methylxanthines	Aptamer, aptamer sandwich assay
Neuroleptics and antidepressants	Enzyme linked biosensory (HRP)
Cytotoxics agents	Antibody competitive assay, antibody sandwich assay, antibody direct assay, aptamer, aptamer sandwich assay
Beta-lactam antibiotics	Electronic, enzyme likned biosenosry (HRP)
Antineoplastics	Aptamer, aptamer sandwich assay
Imidazolic compounds	DNA sensors
Antraciclins and sulphonamides	DNA, DNA-enzyme linked biosensory (HRP)
Tetracyclines and quinolones	Electronic, enzyme likned biosenosry (HRP)

HRP: Horseradish peroxide
Source: Authorship Own (Dec. 2014).

IV. Demonstrative conjuncture

A number of biosensors have been developed with assortment of applications, including environmental and bioprocess control, quality control of food, agriculture, military and more significantly in the field of clinical and diagnostics which can be termed as medical applications. Phytochemicals are one of the major sources of modern medicaments. The research and development of drugs with health applications is always difficult in terms of economy, time limitation and risk of implementing innovative procedures in a bid to combine accuracy, precision, selectivity, sensitivity with simplicity and rapidity. From the portal evidences (articles and patents) and above discussion, the review study confirms that we have a good number of biosensors incorporated to the related fields, those can be replaced with the time consuming critical phases shown in the Figure 1. Conversely, for consolidation of the sensory strategy for use in phytomedical applications, we need to concentrate more on devising biosensors with an innovative perspective.

Conflict of interest

We declare that we have no conflict of interest.

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